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Emile Zuckerkandl, photo by Giacomo Bernardi.

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Fifty-Year Old and Still Ticking.... An Interview with Emile Zuckerkandl on the 50th Anniversary of the Molecular Clock

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Abstract In 1962, a young post-doctoral fellow and a prominent Nobel Prize winner, Emile Zuckerkandl and Linus Pauling, published a seminal paper that described the relationship between the average number of aminoacid replacements and divergence time, known as the molecular clock (Zuckerkandl and Pauling 1962). Fifty years after the original publication, I was fortunate enough to interview Emile Zuckerkandl. We shared thoughts on his life and the historical events that led to the discovery of the molecular clock.

Keywords Molecular clock · Emile Zuckerkandl · Linus Pauling

Interview

In 1962 a young post-doctoral fellow and a prominent Nobel Prize winner, Emile Zuckerkandl and Linus Pauling, published a seminal paper that described the relationship between the average number of aminoacid replacements and divergence time, known as the molecular clock (Zuckerkandl and Pauling 1962). Little did they imagine that the repercussions of this discovery would be, among many other discoveries, one of the pillars of the neutral theory of evolution, the basis for our understanding of the historical meaning of the tree of life, and the timing of the divergence between humans and chimps. For example, coalescent approaches and skyline plots that provide insight on past

population demographics rely on its principles. Thus the consequences of the molecular clock are far-reaching.

Fifty years after the original publication, I was fortunate enough to interview Emile Zuckerkandl. We shared thoughts on his life and the historical events that led to the discovery of the molecular clock. Jane and Emile welcomed me into their elegant home in Palo Alto (Fig. 1). Emile recounted the events leading to the discovery, while Jane peppered the conversation with insights and an incredibly acute memory. Below are excerpts of this conversation.

Giacomo Bernardi: Dear Emile, thank you so much for giving me the opportunity to ask you questions about your scientific and private life. As you know, 2012 marks the 50th anniversary of the first paper on molecular clocks that you wrote with Linus Pauling (Zuckerkandl and Pauling 1962). Before we get into that event, would you like to remind us about your youth, the role of your family in the political and artistic arenas, and your family moving within Europe?

Emile Zuckerkandl: Thank you so much for your interest, even though the events you are alluding to are distant in time now, they have deeply marked me. My youth was interesting in that fate put me in the middle of a society in central Europe that was remarkable through the cultural products that it managed to generate and I had the good luck to grow up in an environment in which these activities were very strongly represented. Also, I lived, of course, through dramatic experiences that were caused by the history of the time and the forces of evil that were at work in central Europe and became so prominent and dominant. I was personally very lucky in what my immediate family and I escaped the worst. In the process, I lost thirteen members of my more extended family. Tragically, they were killed, directly or indirectly through Hitler's

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Fig. 1 Emile Zuckerkandl in his home in Palo Alto, California, with a portrait of Linus Pauling in the background, 3 May 2012 (photo by the author)

activities. Luckily, I had some French family by marriage and that circumstance was a saving grace for the people of my ancestry, namely the Jewish ancestry. Although personally I am not interested in religious matters, I was directly concerned by the Nazi regime targeting one's ancestry which, of course, one can never choose, with consequences that in so many cases led to not only misfortune, but also terrible deaths inflicted among so many people at the time.

GB: So the immediate consequence was that your family moved to France.

EZ: Yes, in fact my father was already in France where he had transferred his activities and had Hitler not come to Austria, still a few years later my mother and I would have joined him in France. Part of my family had been French for a couple of generations and I had been to France, most summers, during my childhood, so France was not really a foreign country to me.

GB: So did you do your undergraduate and graduate studies in France?

EZ: I went to high school mostly in Vienna, but for the last couple of years, in France, and thus got my high school diploma in Paris, at the Lycée Janson de Sailly.

GB: Before we go further into your scientific career, I would like to hear about what influenced your early interest in science. Your family was prominent in the arts and politics, your great grandfather was the advisor of the Crown prince, his daughter, your grandmother, introduced Gustav Mahler to her friend Alma, who was to become his future wife, she included amongst her artist friends Auguste Rodin and Gustav Klimt, and was going to be portrayed by Egon Schiele but for his untimely death to the flu epidemic of 1918, yet you chose a scientific path.

EZ: Well they were also scientifically active people, my father was a biochemist who spent his whole life in

laboratories, and his father was an anatomist at the University of Vienna. On my mother's side, her father, Wilhelm Stekel, was one of the early psychoanalysts in Vienna and wrote many influential books on that field.

GB: You then went on to undergraduate and graduate school?

EZ: After I had fled from Austria to France in order to escape nazism, Germany invaded also France and my parents, my paternal grandmother and I had to flee again. We moved to Algiers, in North Africa, but at the beginning, nobody was sure that the Germans would not invade North Africa. As it turns out Americans landed first and I was able to spend the rest of the war in Algiers, which was French at the time. There, I began to go to the University, but I was expelled because of my Jewish ancestry because of the anti-Jewish laws promulgated by the Vichy government of France that collaborated with the Germans. I could not longer study at the University in Algiers, so as an alternative I elected to go to the one school that was open to me for some strange reason, the conservatory of music in Algiers where I studied piano for a few years.

Yet, as my immediate family's situation was uncertain, my paternal grandmother in particular, Berta Zuckerkandl-Szeps, then in Algiers and particularly threatened, had contemplated fleeing to the United States. My parents' and my friend Walther Meyer, a mathematician who was working with Albert Einstein, looked into finding a scholarship for me to study in the United States. Albert Einstein got interested in my personal fate and helped me obtain that scholarship.

GB: Albert Einstein? Did you ever meet him?

EZ: Yes, I went to visit my friend Walther Meyer at Princeton, and on that occasion paid a little visit on an afternoon to Einstein who was charming. He was so welcoming and kind—I remember his luminous smile.

GB: What an incredible encounter.... So going back to our story....

EZ: Yes, as the war came to an end, I spent one year in Paris and then went to the University of Illinois with that scholarship. I would spend the summers at the Marine Laboratory in Woods Hole. From that activity, I came to write a Doctoral Thesis, and got my PhD in France. I then spent 10 years at the Station Biologique of Roscoff, in western France.

GB: After the PhD you ended up doing a Post Doc with Linus Pauling.

EZ: That is correct. I had never dared thinking of such a possibility, but it was a close friend of mine, J. Gordin Kaplan, who had come to visit the Station in Roscoff, where I worked at the time, who told me that I must make a move to come to the US and study there.

GB: Do you remember how you first met Pauling and what was the occasion of this encounter?

EZ: It happened during a trip of Linus Pauling to Paris. I wrote him to ask if I could meet with him, and he answered positively. So I went from Roscoff to Paris, and he was favorable to the idea that I would come to Cal Tech and work under him.

GB: So when you moved to Cal Tech, was there already the idea for the lab to work on what was to become the field of Molecular Evolution? What was the atmosphere in Pauling's lab?

EZ: So far as I remember there was nothing ongoing in Molecular Evolution, a field that was just forming at the time.

GB: In 1962 there is this paper that the two of you wrote that relates protein evolution with time, which is completely different than anything else that had been done before, how did the idea come about? Was there a discussion between the two of you? Do you remember how the idea of a molecular clock came about?

EZ: For the molecular clock, I believe I can say that I evolved ideas quite independently. That applies in particular to the idea of the molecular clock—to the idea as well as to the name. Of this independence I am completely certain, even though one may infer from the relative modesty of personal recognition that I received that this independence of my theoretical developments was not generally recognized. In fact I developed the matter conceptually during a temporary stay at the Marine Laboratory of Woods Hole in Massachusetts, where I spent some time in the later months of the year. There was no input from Pauling or from anyone else. At that time, it was just the beginning of protein sequencing, few people in the world had access to any sequences at all. Since some protein sequences were available, or rather tryptic peptides, Pauling suggested to compare these sequences. At that time globin protein sequences were done in Braunitzer's and Schroeder's labs and Max Delbruck brought back sequences from Braunitzer's lab. Human sequences could then be compared with Gorilla sequences.

Pauling was a big name and was commonly invited by Journals to submit manuscripts, but he himself was less into science as he was then deeply involved in the political arena with his anti-nuclear stance. So he came to me and said that he was invited to write a paper and if I could write it. At that time most papers were written on invitation, so this was not unusual. The usual pattern of things was that I would write a paper and I would submit it to him. He would then make some changes that would be moderate, and then the paper would come out as I conceived it.

GB: This brings me to the follow up paper of 1965 where you expanded the original 1962 manuscript (Zuckerlandl and Pauling 1965). There, you cite Hegel's *aufgehoben*, I suspect that this is a personal touch that you

inserted in the manuscript, and I don't know if Linus Pauling even saw that line, or did he?

EZ: Oh yes he saw that line, he left it in, but this sort of consideration arose in my mind surely as a consequence of discussing things with my father who was very philosophically minded.

GB: I have a question about the scientific process. Since the discovery of the molecular clock 50 years ago, the details have been refined, but the basic concept is still here and its use is increasing if anything. Yet how did the original discovery come about, was it a gradual discovery, or was there a *Eureka* moment where all of a sudden you noticed a pattern of divergence in those globins?

EZ: No, it seemed natural to wonder whether the succession of changes that were obviously taking place through evolution, and not exclusively by any means but to a large extent were then known as attributable primarily to exchanges of individual bases in genes or aminoacids in corresponding proteins, that such changes came out with a frequency that could be represented by means that were not, as such, meaningless, namely that different means of substitution rates of the components of the informational macromolecules of biological objects would in fact be characteristics that should be analyzed and evaluated properly.

GB: Your discovery became far-reaching and entire programs are designed around the concept, and thousands of papers have used molecular clocks as the basis for their more important conclusions. When you first wrote this paper did you think that your idea would become so widely used?

EZ: I was not thinking in those terms. The concept just seemed to me as a natural aspect of Evolution.

GB: Currently the field has reached powers that were unimaginable 50 years ago, with personal genome sequencing and so forth, yet the basic concept of the molecular clock remains, do you have any thoughts about this?

EZ: The molecular clock cannot be accurate in its details, in other words it would be illusory to think that mutations would actually happen at nearly identical intervals, the question then is, are the mean values of these intervals meaningful? I made the assumption that, yes, they characterize these molecules and that one could reach reasonable estimates of the actual age of various important stages in the development of this type of analyses.

GB: While now there are different flavors of the concept, with strict and relaxed clocks, the idea resulted in a broad array of studies.

EZ: Yes, perhaps coming to that field at the right moment and yet from the outside permitting a fresh look at things was helpful at that time.

GB: To wrap up our conversation I would like to know how the idea of creating the Journal of Molecular Evolution arose?

EZ: That was actually not my idea. That was the idea of the leader of Springer Verlag at the time, Conrad Springer. He sensed that Molecular Evolution was an upcoming field and was eager to start a journal. He had considered Tom Jukes as editor in chief, but later went to a meeting in Belgium, that I attended, and offered me the position, which I accepted.

To conclude our interview with Jane and Emile Zuckerkandl, we toasted with a glass of Calvados, an apple based liqueur that is traditional of western France, fittingly including Roscoff.

Acknowledgments I would like again to thank Emile and Jane Zuckerkandl for inviting me to share a moment of their life, and Giorgio Bernardi for being the impetus of this interview.

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